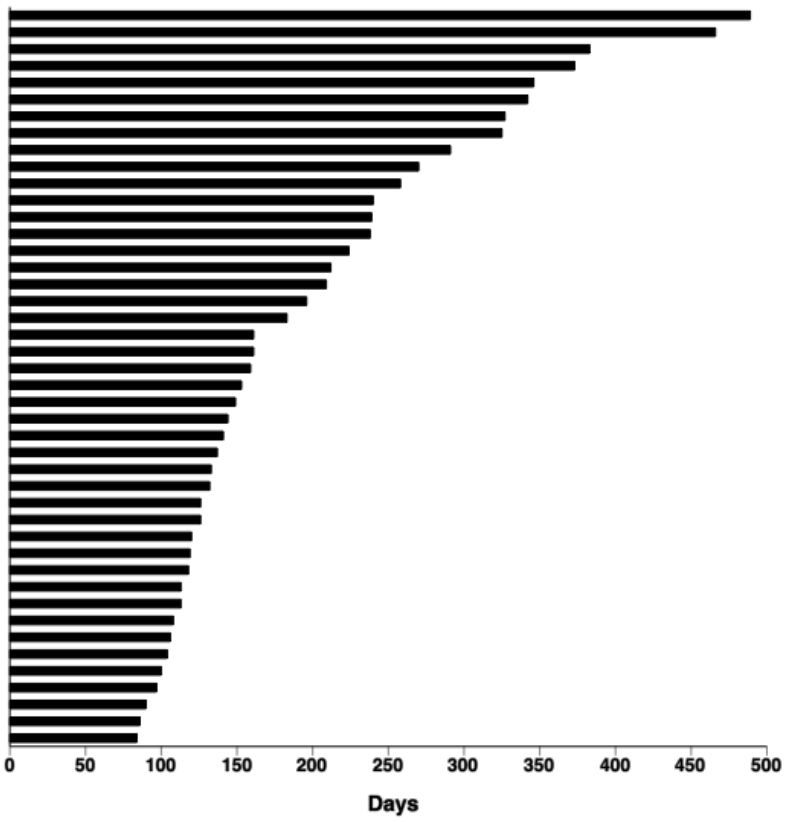
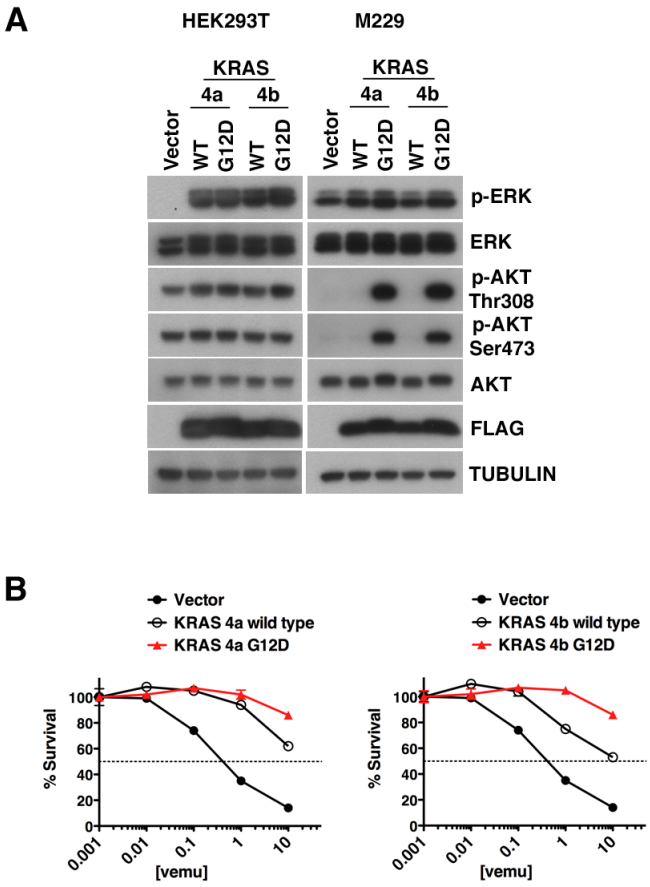
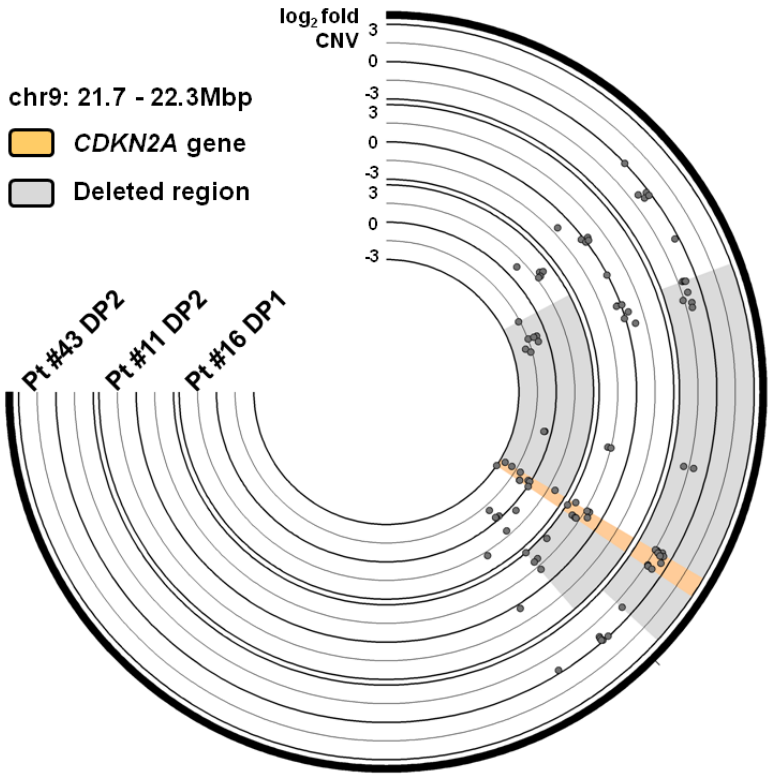


Supplementary Figure S1. Distribution of progression-free survival (PFS, x-axis) among individual patients (y-axis) whose melanoma biopsies were studied.

Supplementary Figure S2. Sanger re-sequencing of 108 DP-specific mutations called by the WES mutation-calling pipeline. Slide numbers correspond to those found in Supplementary Table S4. Slides 1 to 108 attached separated.

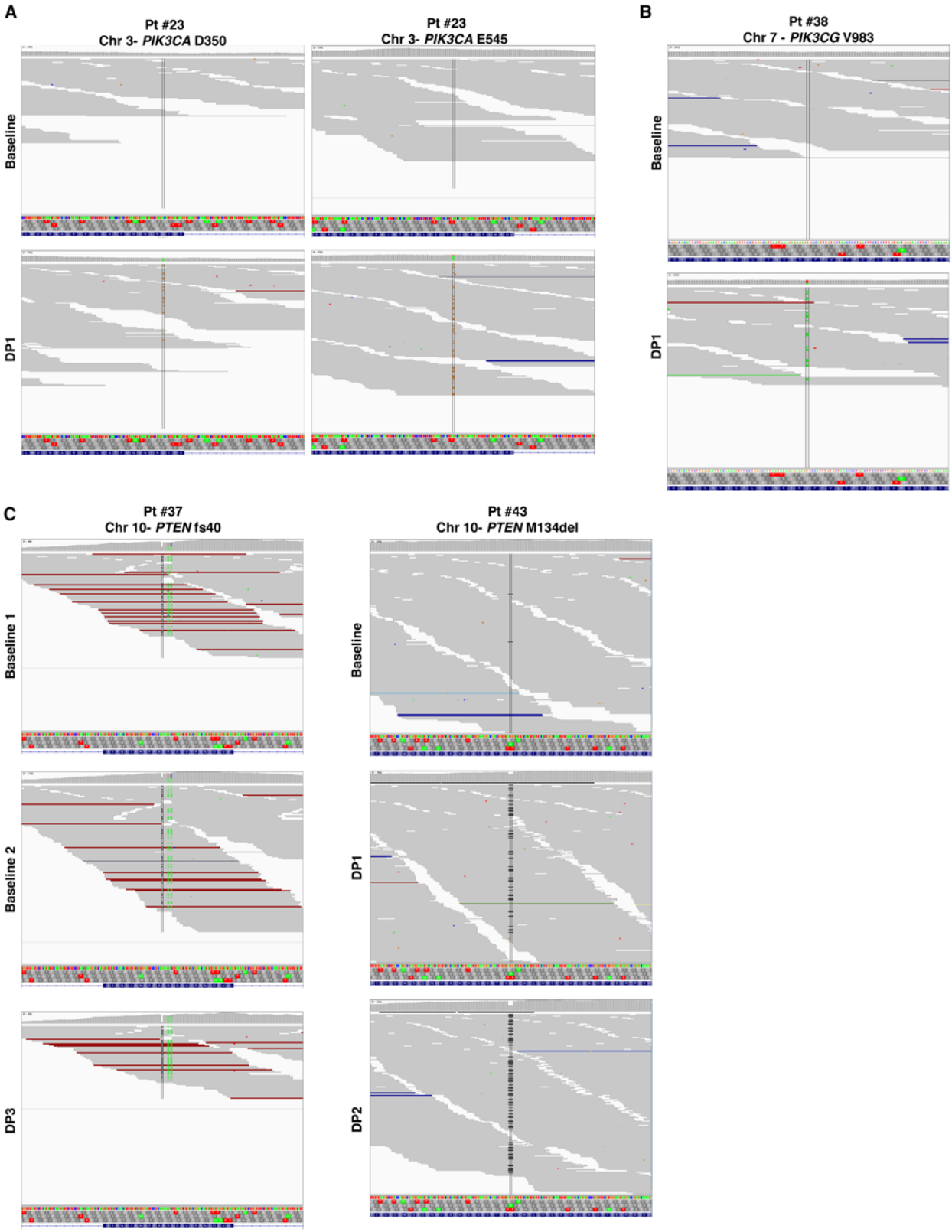


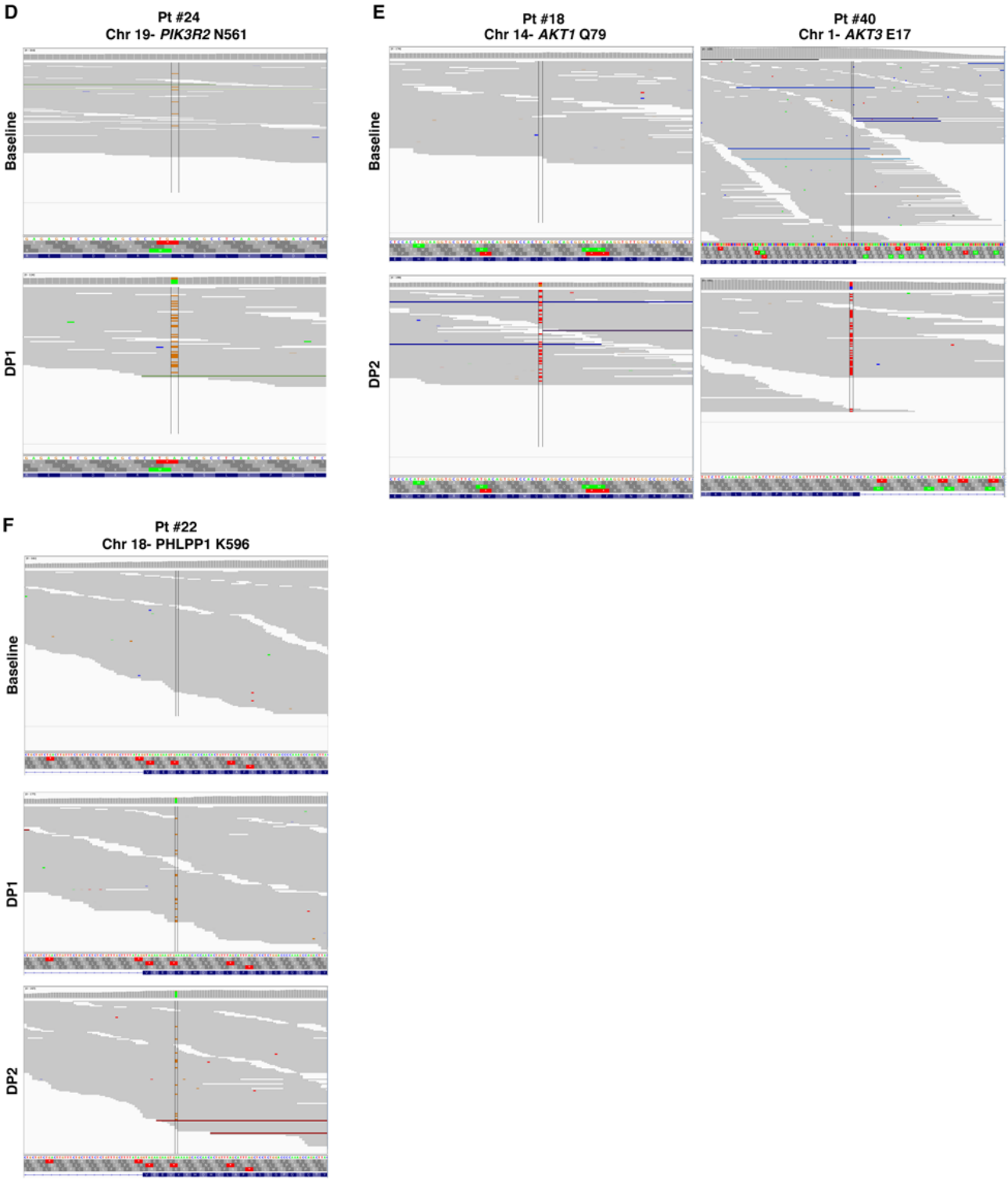
Supplementary Figure S3. Impact of mutant KRAS 4a/b isoforms on the MAPK and PI3K-AKT pathways and melanoma survival in the presence of vemurafenib. A, Indicated FLAG-tagged constructs were transiently transfected into HEK293T cells (left) or packaged into lentiviral particles and transduced stably into M229 melanoma cells (right). The levels of indicated proteins were probed by immunoblotting (TUBULIN, loading control). **B,** The effects of wild type or G12D versions of KRAS4a (left) or 4b (right) on BRAF inhibitor sensitivity (vemu, vemurafenib) in the ^{V600E}BRAF melanoma cell line, M229, as assessed by three-day MTT assays (error bars, SEM).



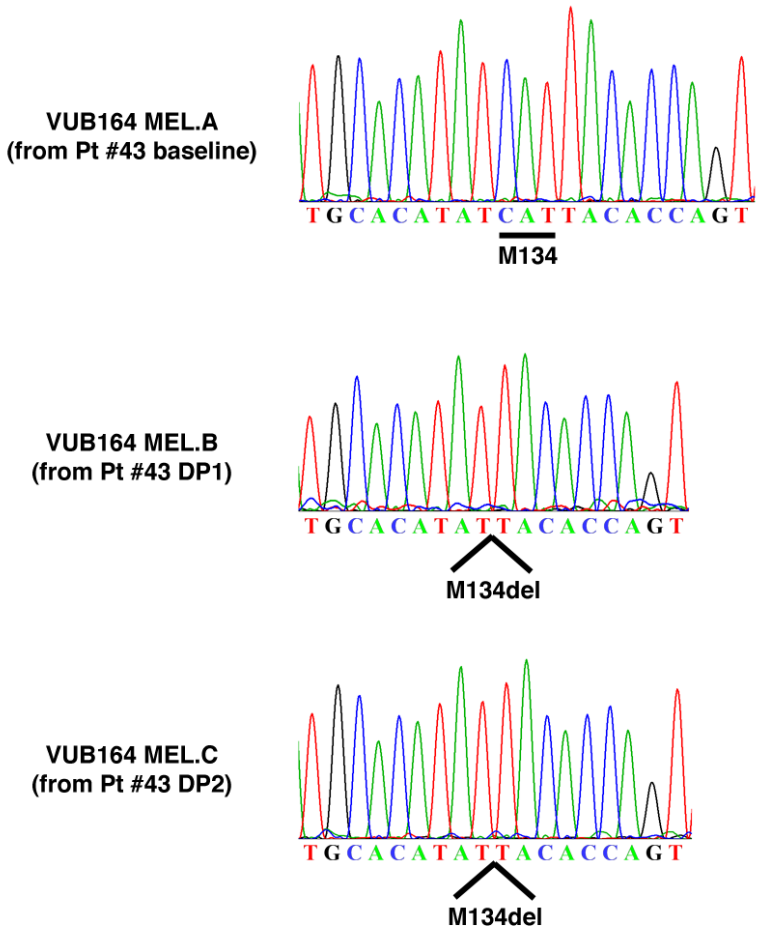
Supplementary Figure S4. Recurrent *CDKN2A* loss visualized by Circos.

Patient and DP tumor numbers (see Supplementary Table S2) indicated along concentric tracks.

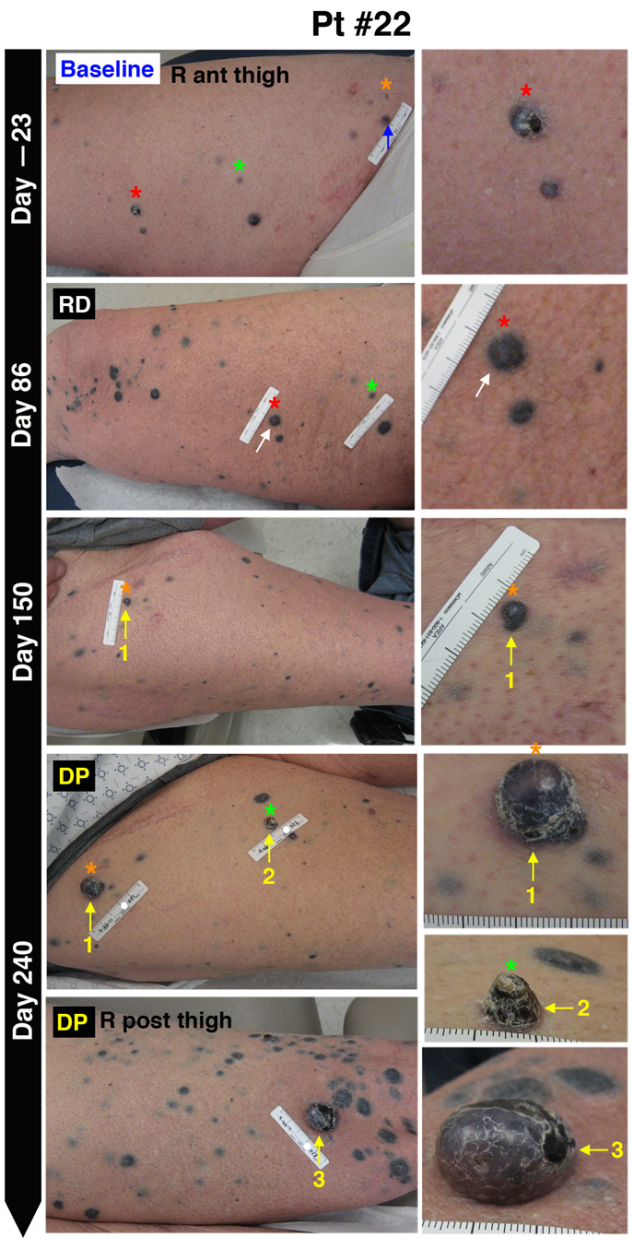

A
Pt #23
Chr 3- PIK3CA D350
Pt #23
Chr 3- PIK3CA E545
Baseline
DP1
B
Pt #38
Chr 7 - PIK3CG V983
Baseline
DP1
C
Pt #37
Chr 10- PTEN fs40
Pt #43
Chr 10- PTEN M134del
Baseline 1
Baseline 2
DP3
Baseline
DP1
DP2


D
Pt #24
Chr 19- PIK3R2 N561
Baseline
DP1
E
Pt #18
Chr 14- AKT1 Q79
Pt #40
Chr 1- AKT3 E17
Baseline
DP2
F
Pt #22
Chr 18- PHLPP1 K596
Baseline
DP1
DP2

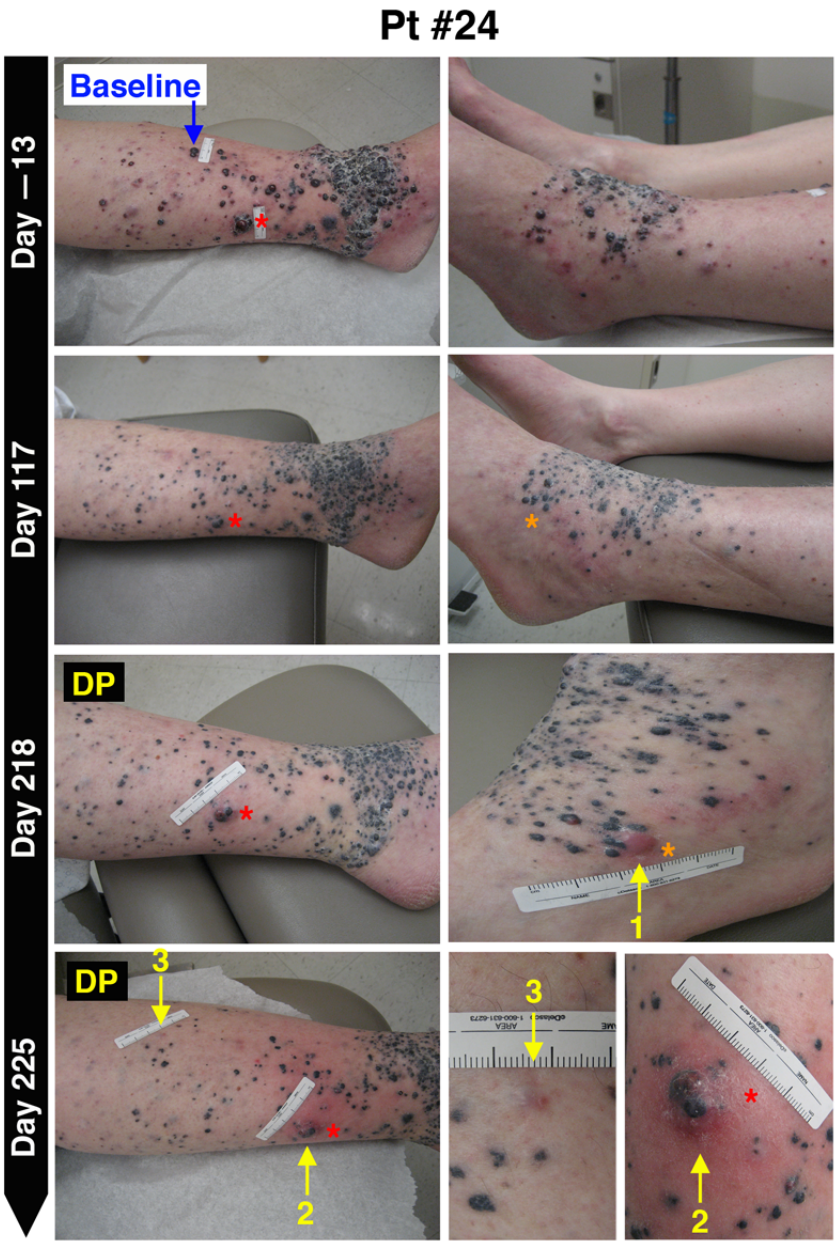
Supplementary Figure S5. Integrated Genome View (IGV) snapshots of reference and variant allelic frequencies in PI3K-PTEN-AKT pathway (see Supplementary Table S4). DP-specific or -enriched nucleotide variants resulting in PIK3CA D350G and E545G (**A**), PIK3CG V983E (**B**), PTEN frameshift at amino acid 40 and deletion of M134 (**C**), PIK3R2 N561D (**D**), AKT1 Q79K and AKT3 E17K (**E**), and PHLPP1 K596E (**F**).



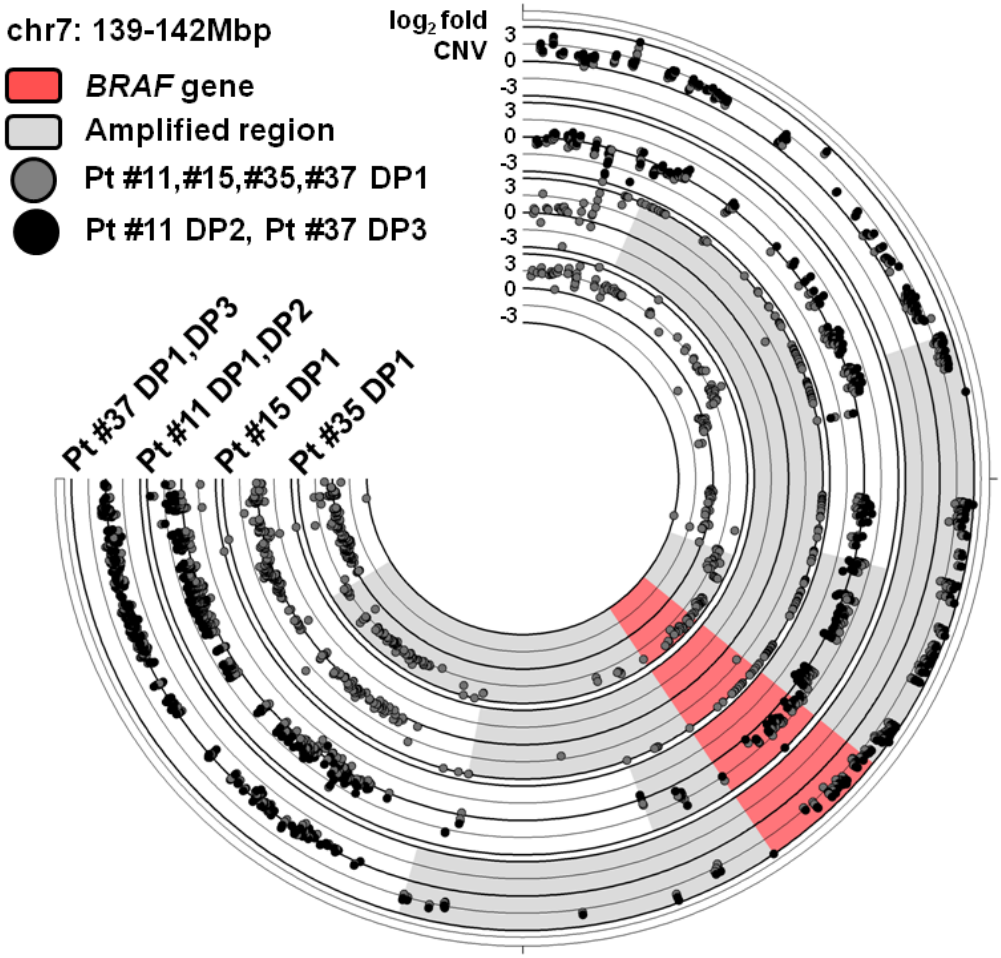
Supplementary Figure S6. Sanger sequencing of *PTEN* in short-term melanoma cultures derived from tumor biopsies of Patient #43. Consistent PTEN cell line vs. corresponding tumor *PTEN* status. A *PTEN* M134 deletion was observed only in cell lines established from DP tumors.



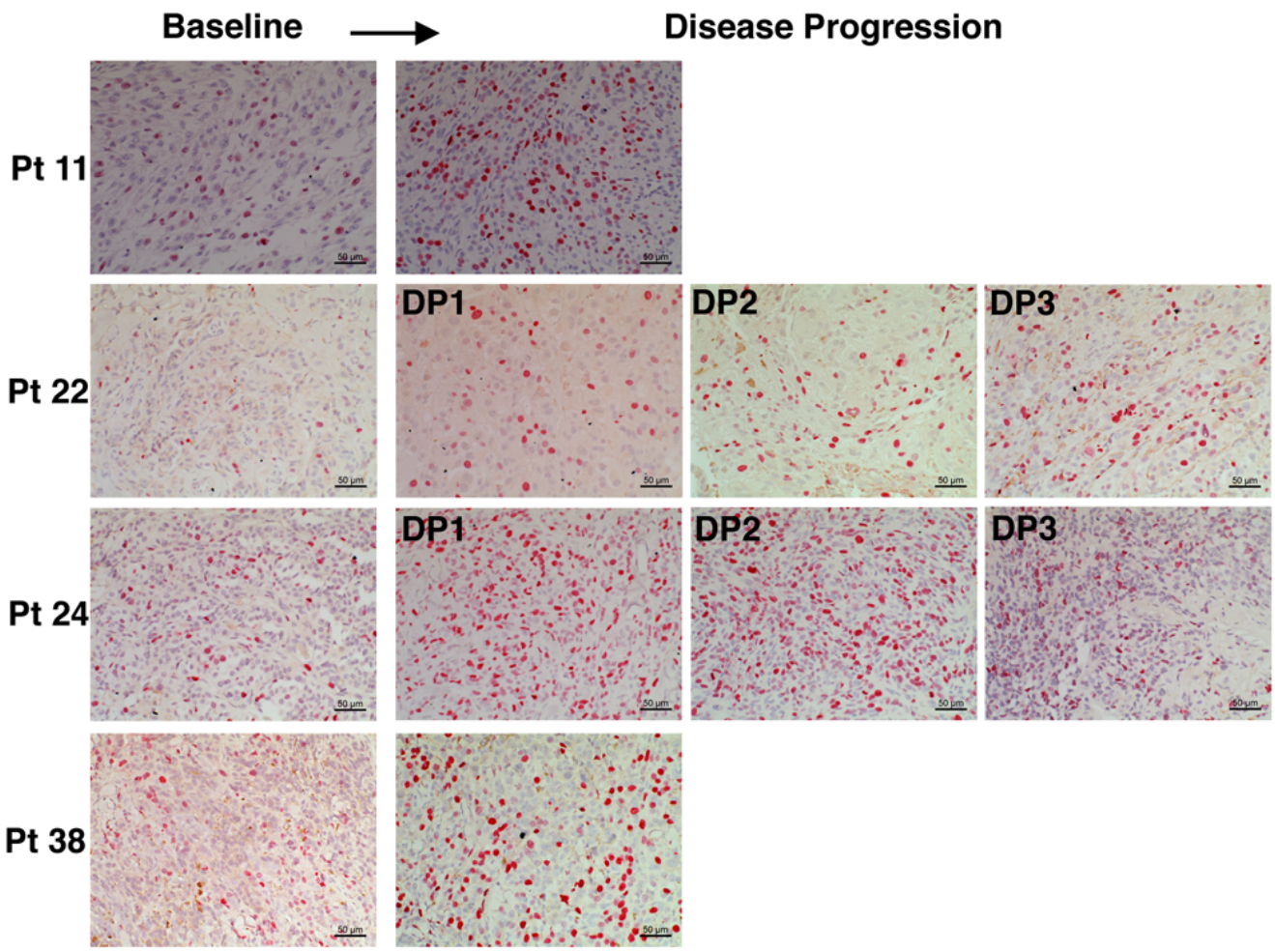
Supplementary Figure S7. Time course of metastatic melanomas to the skin in patient #22 responding and developing acquired resistance to the BRAF inhibitor vemurafenib. DP1 was first noted on Day 150 of treatment, whereas DP2/3 were noted on Day 240. Asterisks of the same color denote the same positions in distinct photographs. RD, Residual Disease. DP, disease progression.



Supplementary Figure S8. Time course of metastatic melanomas in patient #24 responding and developing acquired resistance to dabrafenib. DP1/2 was first noted on Day 218 of treatment, whereas DP3 were noted on Day 225. Asterisks of the same color denote the same positions in distinct photographs. DP, disease progression.



Supplementary Figure S9. Recurrent DP-specific mutant *BRAF* amplifications visualized by Circos. Selected examples from Supplementary Table S2 shown, highlighting similar alterations (amplicon size) noted in distinct DP tumors from the same patients (#11, #37).



Supplementary Figure S10. Melanomas with acquired BRAF inhibitor resistance biopsied during disease progression display increased proliferation compared with their patient-matched baseline melanomas. Representative examples of Ki-67 IHC shown (bar, 50 μM).